2017-03-17

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Twin Res Hum Genet. 2014 Dec;17(6):553-62.
http://doi.org/10.1017/thg.2014.58
http://hdl.handle.net/10616/45603

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DOI: https://dx.doi.org/ 10.1017/thg.2014.58

Title page

Exposure to air pollution from traffic and neurodevelopmental disorders in Swedish Twins

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Running title:

Exposure to air pollution and neurodevelopmental disorders

Abstract

Background Recent studies have reported associations between air pollution exposure and neurodevelopmental disorders in children but the role of pre- and postnatal exposure has not been elucidated. **Aim** We aimed to explore the risk for autism spectrum disorders (ASD) and attention-deficit hyperactivity disorder (ADHD) among children in relation to pre- and postnatal exposure to air pollution from road traffic. **Method** Parents of 3,426 twins born in Stockholm during 1992-2000 were interviewed when their children were 9 or 12 years old regarding symptoms of neurodevelopmental disorders. Residence time weighted concentrations of particulate matter with diameter<10μm (PM_{10}) and nitrogen oxides (NO_x) from road traffic were estimated at participants' addresses during pregnancy, first year and ninth year of life using dispersion modeling, controlling for seasonal variation. Multivariate regression models were used to examine the association between air pollution exposure and neurodevelopmental outcomes, adjusting for potential confounding factors. **Result** No clear or consistent associations were found between air pollution exposure during any of the three time windows and any of the neurodevelopmental outcomes. For example, a 5- 95% difference in exposure to NO_x during pregnancy was associated with odds ratios (ORs) of 0.92 (95% confidence interval 0.44-1.96) and 0.90 (0.58-1.40) for ASD and ADHD, respectively. A corresponding range in exposure to PM_{10} during pregnancy was related to ORs of 1.01 (0.52-1.96) and 1.00 (0.68-1.47) for ASD and ADHD. **Conclusion** Our data do not provide support for an association between pre- or postnatal exposure to air pollution from road traffic and neurodevelopmental disorders in children.

Key words:

air pollution, PM_{10}, NO_x, autism, ADHD, twins

Abbreviations used:

Attention deficit/hyperactivity disorder (ADHD); autism spectrum disorders (ASD); Autism-Tics, ADHD, and other Comorbidities inventory (A-TAC); Child and Adolescent Twin Study in Sweden (CATSS); confidence interval (CI); Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV); generalized estimating equation (GEE); nitrogen oxides (NO_x); odds ratio (OR); particulate matter (PM); small-area market statistics (SAMS).

Introduction

Neurodevelopmental disorders are relatively common and pose a substantial challenge to society (Froehlich et al., 2007; Jarbrink, Fombonne, & Knapp, 2003; Kogan et al., 2008; Newton, 2012). For some conditions the diagnosis rates have increased but the reasons behind these apparent time trends remain largely unknown. Improved awareness and widened diagnostic criteria may contribute, such as for attention deficit/hyperactivity disorder (ADHD) and autism spectrum disorders (ASD), but probably do not explain the whole increase. Both ADHD and ASD are childhood onset chronic conditions of moderate to high heritability (Anckarsater et al., 2011; Martin, Scourfield, & McGuffin, 2002; Parr et al., 2011). However, their precise etiologies remain enigmatic, and the role of environmental factors acting as triggers or contributors to general vulnerability should not be disregarded (Sandin et al., 2014).

Epidemiological and experimental studies indicate that exposure to air pollution from road traffic may induce systemic inflammation and increase the risk of several diseases related to inflammation, such as asthma, allergy, and cardiovascular diseases (Mills et al., 2009; Nordling et al., 2008; Panasevich et al., 2009). Systemic inflammation can also contribute to neuronal injury and affect the development of central nervous system (Hagberg & Mallard, 2005). Recent epidemiological studies have shown associations between exposure to air pollution from road traffic or other sources and adverse neurodevelopmental effects in children (Becerra, Wilhelm, Olsen, Cockburn, & Ritz, 2013; Calderon-Garciduenas et al., 2011; Dix-Cooper, Eskenazi, Romero, Balmes, & Smith, 2012; Guxens et al., 2012; Jung, Lin, & Hwang, 2013; Morales et al., 2009; Siddique, Banerjee, Ray, & Lahiri, 2011; Windham, Zhang, Gunier, Croen, & Grether, 2006; Volk, Hertz-Picciotto, Delwiche, Lurmann, & McConnell, 2011; Volk, Lurmann, Penfold, Hertz-Picciotto, & McConnell, 2013; Vrijheid et al., 2012). However, more studies are needed to assess causality, particularly since the

association may be confounded by socioeconomic and sociodemographic characteristics (Bhasin & Schendel, 2007; Flouri, Mavroveli, & Tzavidis, 2012). Furthermore, it is not known if there are specific periods of increased vulnerability.

The primary objective of this study was to investigate the relation between exposure to air pollution from road traffic and the risk of neurodevelopmental disorders in children, especially ASD and ADHD. In particular, the influence of exposure during potentially important time windows, such as the fetal and infancy periods, was in focus.

Materials and methods

Study population

The children were participants from the Child and Adolescent Twin Study in Sweden (CATSS), an ongoing longitudinal cohort study that targets all twins born in Sweden since July 1, 1992 (Anckarsater et al., 2011). In this project the twins born 1992-2000 were included. Parents of 17,220 9-year-old twins were contacted and interviewed regarding their children's somatic and mental health as well as social environment (Figure 1). During the first three years of the study, 12-year-old twins were also included. Since the air pollution exposure assessment methodology was restricted to Stockholm County, 4,980 twins born in this area were selected and 3,426 completed the neurodevelopmental assessment (response rate 68.8 %). The study was approved by the Regional Ethical Review Board in Stockholm, Sweden.

[insert Figure 1 here]

Health outcome assessment

Children's neurodevelopmental outcomes were measured using the Autism-Tics, ADHD, and other Comorbidities inventory (A-TAC) telephone interview developed at the Institute of Neuroscience and Physiology, Child and Adolescent Psychiatry, Gothenburg University (Hansson et al., 2005). A-TAC consists of 178 symptom questions from a lifetime perspective and is designed as an open-access and comprehensive tool for screening childhood ASD and other targeted disorders based on DSM-IV criteria. Response options for each question were coded as 0 for "No", 0.5 for "Yes, to some extent", and 1.0 for "Yes". In two previous validation studies, autistic-like traits were assessed by the sum scores of 12 items (based on DSM-IV criteria) or 17 items (by adding one additional item from the flexibility and two additional items each from the language and social interaction modules) (Hansson et al., 2005;

Larson et al., 2010). To comprise the primary symptoms of ADHD, scores of 18 (based on DSM-IV criteria) or 19 items (by adding one additional item from the impulsivity module) were summed up. Cut-off values for the sum scores with high sensitivity and specificity from previous validation studies were used in the current study to resemble the probabilities of clinical diagnoses and severity of both diseases: ASD≥4.5 for DSM-IV criteria and for the lower cutoff value of extended diagnostic criteria, ASD≥8.5 for the higher cutoff value of extended diagnostic criteria, ADHD≥8 for DSM-IV criteria, ADHD≥6 and ADHD≥12.5 for the lower and higher cutoff values of extended diagnostic criteria. Detailed information on the psychometric properties of the A-TAC is provided elsewhere (Anckarsater et al., 2011; Hansson et al., 2005; Larson et al., 2010).

Exposure assessment

The air pollution concentrations at residential addresses during mother's pregnancy, child's first year of life and the year before the neurodevelopmental assessment were estimated by dispersion models, described in detail elsewhere (Bellander et al., 2001; Gruzieva et al., 2012). Briefly, the residential history of the study subjects was obtained from taxation authorities and geocoded using a property register maintained by the Swedish mapping, cadastral and land registration authority. The address information was linked with historical emission databases to obtain annual average levels of nitrogen oxides (NO_x) and particulate matter with less than 10 μm of diameter (PM_{10}). Residence time weighted NO_x and PM_{10} concentrations related to road traffic emissions were calculated for each trimester and over the mother's pregnancy period, the child's first year and 9^{th} year of life. Furthermore, daily 24 hour mean NO_x and PM_{10} levels from suburban stations were used to calculate the NO_x and PM_{10} levels during each trimester of the pregnancy, which were taken into account in sensitivity analyses. Imputation for missing values of NO_x and PM_{10} in the trimester-specific analyses was

143 performed using predictions from rooftop measurements of both pollutants from a monitoring
144 station in the center of Stockholm.

145 ## Other covariates

146 Information on gender (male / female), parity (first / second / third / fourth or later),
147 gestational age (<37 weeks / ≥37weeks), birth weight (<2,500g / ≥2,500g), maternal age at
148 birth (<25 / 25-29 / 30-34 / ≥35yrs old), maternal smoking during pregnancy (no/ 1-9
149 cigarettes per day/ ≥10 cigarettes per day) was obtained from the Medical Birth Register
150 ("The Swedish Medical Birth Register: a summary of content and quality," 2003). Using the
151 Longitudinal integration database for health insurance and labor market studies (LISA),
152 originally from Statistics Sweden, we obtained individual-level socioeconomic data such as
153 maternal marital status (married or cohabiting / single), parental education (≤9yrs / 10-12yrs
154 / >12yrs) and family disposable income during mother's pregnancy, child's first year of life
155 and 9th year of life with adjustment for inflation and family size. Furthermore, a neighborhood
156 deprivation index was used to estimate area-based socioeconomic characteristics at birth year
157 (Sariaslan et al., 2013). Neighborhood was defined by the small-area market statistics (SAMS)
158 based on regional population density ("Post codes and SAMS atlas," 2013). Data including
159 information from Statistics Sweden on welfare beneficiaries, unemployment, immigrants,
160 divorce rate, income, education, residential mobility, and criminal conviction rate were linked
161 with each SAMS unit to calculate a neighborhood deprivation index using principal
162 component analysis. Information on comorbidity with severe chromosome abnormalities,
163 neural tube defects and other neurological diseases including epilepsy and cerebral palsy (see
164 Table S1) was obtained through parent-report in CATSS as well as from the National Patient
165 Register according to diagnoses from hospital discharge or outpatient department visits.

166 ## Statistical analysis

Generalized estimating equations (GEE) with exchangeable correlation structure in combination with Huber-White sandwich estimator for the standard errors to adjust for clustering of observations within twin pairs were used to estimate odds ratios (OR) and 95% confidence intervals (CI) for each neurodevelopmental outcome associated with a 5^{th} to 95^{th} percentile increase in NO_x or PM_{10} on the entire sample (Carlin, Gurrin, Sterne, Morley, & Dwyer, 2005). We used a directed acyclic graph to determine potential confounders for the ORs (Greenland & Brumback, 2002). A series of models were run step-wise to assess the OR changes by further adjustment for potential confounders, however, only crude and adjusted models including all potential confounders ($p<0.20$) are presented.

Cutoff values validated in two previous studies were used as outcomes in all analyses (Hansson et al., 2005; Larson et al., 2010). Furthermore, we added a general neurodevelopmental outcome defined as scoring above any ASD or ADHD-related cutoff values due to the high co-occurrence of both diseases. Sensitivity analyses were performed using air pollution exposure during child's 9^{th} year of life and during each trimester of pregnancy controlling for seasonal effect, and by defining cases with comorbidity of severe chromosome abnormality, neural tube defects and other neurological diseases including epilepsy and cerebral palsy (See table S1). Furthermore, a subset of children whose mothers responded at the interview was analyzed to avoid reporting bias among different family members.

The statistic package STATA version 12 (Stata Corp., College Station, TX, USA) was used for all analyses.

Results

Table 1 lists characteristics of the study population. Eligible subjects were on average 10.3 years of age; 76% of mothers did not smoke during pregnancy, and only 6% of the families had less than 9 years of education. Children with neurodevelopmental disorders were predominantly male, more likely to be born in a lower educated family with at least one parent from Scandinavian countries, exposed to maternal smoking during pregnancy, and diagnosed comorbidity with severe chromosome abnormalities, neural tube defects and other neurological diseases including epilepsy and cerebral palsy. The non-responding twin parents showed some socio-demographic differences compared to those included in the analyses, such as younger maternal age, more single mothers, lower parental education and family income, as well as higher neighborhood deprivation.

[insert Table 1 here]

Figure 2 shows air pollutant levels during pregnancy, child's first and 9^{th} years of life. Yearly average levels of NO_x from local traffic dropped from 12.7μg/m^3 to 5.4μg/m^3 during the observation period, which is reflected in reduced levels from pregnancy/infancy to the 9^{th} year of life. On the other hand, the yearly average levels of PM_{10} were relatively constant (3.3-4.2μg/m^3). NO_x was closely correlated with PM_{10} (all p-values<0.001, r^2>0.7) when comparing over the study period as both have local traffic as the major source. However, there were only moderate correlations (all p-values<0.001, r^2<0.4) between pollutants during the 9^{th} year of life and other study periods (see Figures S1a and S1b).

[insert Figure 2 here]

The risks of ASD and ADHD using different cutoff values were not consistently associated with exposure to NO_x or PM_{10} at any age (Figure 3 and Table 2). For example, exposure to

211 NO_x during the first year of life was not associated with ASD (OR 0.86, 95% CI 0.44-1.67) or
212 ADHD (OR 1.06, 95% CI 0.71-1.59), after adjusting for child gender, parity, and other
213 relevant covariates. Likewise, exposure to PM_{10} during first year of life was not related to
214 ASD (OR 0.95, 95% CI 0.56-1.62) or ADHD (OR 1.06, 95% CI 0.75-1.52). A lack of
215 association was also observed for air pollution exposure during pregnancy. Results were
216 similar using the dimensional outcomes for ASD and ADHD (data not shown). It should be
217 noted that there was a substantial overlap between the diagnoses, e.g. 82 of the 109 children
218 with ASD also had ADHD.

219 [insert Figure 3 and table 2 here]

220 When exposure to air pollutants for each trimester of the pregnancy controlling for seasonal
221 effect and during the child's 9^{th} year of life were evaluated separately, similar findings were
222 found with no consistent associations for most neurodevelopmental outcomes related to
223 traffic-air pollutant levels (Tables S3-S5). However, it is noteworthy that an inverse relation
224 was observed between air pollution exposure during 2^{nd} and 3^{rd} trimesters and ASD as well as
225 ADHD using cutoff values based on DSM-IV criteria. We also did a sensitivity analysis by
226 re-defining cases comorbid with chromosome abnormality or neurological diseases (Table S6).
227 The ORs in those analyses tended to be lower, but still no statistically significant association
228 was found. In sub-analyses we assessed all twins whose mothers answered the telephone
229 interview from CATSS and similar findings were found for all outcomes (Table S7).

Discussion

This study did not indicate an association between exposure to NO_x or PM_{10} from traffic during pregnancy or first year of life and neurodevelopmental disorders in children. For specific subgroups and diagnoses, there were some associations but no consistent patterns were evident. This also holds true for analyses related to exposure during certain time windows.

There is limited evidence on air pollution exposure and neurodevelopmental disorders in children (Becerra et al., 2013; Calderon-Garciduenas et al., 2011; Dix-Cooper et al., 2012; Guxens et al., 2012; Jung et al., 2013; Morales et al., 2009; Siddique et al., 2011; Windham et al., 2006; Volk et al., 2011; Volk et al., 2013; Vrijheid et al., 2012). Windham et al (2006) reported a positive relation between the distribution of hazardous air pollutants at birth addresses and ASD among children in California. Other studies in California found that living close to freeways and traffic-related air pollution in mother's late pregnancy or child's first year of life were associated with an increased risk for autism (Volk et al., 2011; Volk et al., 2013). Siddique et al (2011) compared children living in New Delhi urban area with children living in rural areas and showed that ADHD was positively correlated with current PM_{10} levels. Air pollutants may induce systematic inflammation, which could be a possible mechanism mediating these effects (Block & Calderon-Garciduenas, 2009; Calderon-Garciduenas et al., 2008).

The results of our study did not indicate that air pollution has an effect on the risk of neurodevelopmental disorders, even when time windows were considered during fetal life and infancy. The apparently discrepant results compared to some earlier studies could have several explanations. Firstly, relatively low levels of air pollution may contribute to the absence of an association and make it difficult to compare with other study settings. For

example, the local traffic related PM_{10} concentrations during participants' first year of life in Stockholm was only 3.9 $\mu g/m^3$ and the long-range transported PM_{10} in this part of Sweden has a yearly average level of around 10 $\mu g/m^3$ (Gidhagen, Omstedt, Pershagen, Willers, & Bellander, 2013). The roof top levels for PM_{10} in central Stockholm have been relatively constant during 1994-2012 (Burman & Norman, 2013). However, these levels are considerably lower than in the study areas of California described above (mean value at 25±7.2 $\mu g/m^3$ in one study and 36.3±6.1 $\mu g/m^3$ in another study) (Becerra et al., 2013; Volk et al., 2013) . Furthermore, associations may exist between the socioeconomic status at individual or neighborhood-level and the risk for neurodevelopmental or behavioral problems (Bhasin & Schendel, 2007; Flouri et al., 2012). Maternal smoking correlates with socioeconomic factors such as education and income (Kabir, Connolly, & Alpert, 2011; Laaksonen, Rahkonen, Karvonen, & Lahelma, 2005), and may contribute to this association. The earlier studies (Calderon-Garciduenas et al., 2011; Guxens et al., 2012; Siddique et al., 2011; Windham et al., 2006; Volk et al., 2011; Vrijheid et al., 2012) did not always adjust for neighborhood deprivation as well as individual socioeconomic characteristics and smoking during pregnancy, which suggests there could be some residual confounding.

We found inconsistent associations between air pollution in late pregnancy and decreased risk of ASD and ADHD using cutoff values based on DSM-IV criteria. Even though the sample size was relatively large with 3426 subjects, the number of children who scored above the cutoff values for some neurodevelopmental outcomes was low, contributing to statistical uncertainty of the risk estimates.

Strengths of the study include a population-based sample of twins and data linkage to Swedish national registries, which include baseline birth-related and socioeconomic information before disease onset. Secondly, we investigated both ADHD and ASD because of the high degree of comorbidity between the two conditions. Furthermore, we analyzed

neurodevelopmental disorders categorically based on DSM-IV criteria and the additional cutoff values according to previous validation studies (Hansson et al., 2005; Larson et al., 2010). Thirdly, we included different trimesters during pregnancy, first year and 9th year of life using the validated dispersion modeling together with data on road traffic emissions while previous studies reported effects from either prenatal or post-natal air pollution exposures.

There are also several potential limitations of the study. One is that the occurrence of neurodevelopmental outcomes may have differed in children participating in CATSS with completed A-TAC assessment and those in the general population. Two Swedish studies found that children of immigrant parents had impaired psychological health (Gillberg, Steffenburg, Borjesson, & Andersson, 1987; Magnusson et al., 2012; Van Leeuwen, Nilsson, & Merlo, 2012), however the occurrence of neurodevelopmental disorders in our study was lower in families with both parents from outside of Scandinavian countries. The data linkage to other registers allowed us to acquire additional data on the CATSS non-responders, which indicated that children enrolled in the study had higher familial socioeconomic status. Another possible limitation is the assessment of the neurodevelopmental outcomes, which might have created some misclassification (Ragland, 1992). Most earlier studies attempted to evaluate outcomes as discrete scores; however, our data was highly skewed on all outcomes. Our power was limited for analyses of sub-dimensional ASD/ADHD measures. Furthermore, for the exposure time measured during child's 9th year of life, the air pollution assessment may actually have occurred after disease onset.

Conclusion

We found no support for the hypothesis that traffic-related air pollution is associated with an increased risk for neurodevelopmental disorders in children. Comparatively low air pollution levels and a limited statistical power for some outcomes may contribute to explaining the results.

Financial support

Financial support was provided through the Swedish Research Council for Health, Working Life and Welfare (FORTE 2012-0573) , the Swedish Research Council (VR) 2011-3060, VR in partnership with FORTE, FORMAS and VINNOVA [Cross-disciplinary research program concerning children's and young people's mental health], VR through the Swedish Initiative for Research on Microdata in the Social And Medical Sciences (SIMSAM) framework grant no. 340-2013-5867, HKH Kronprinsessan Lovisas förening för barnasjukvård, and the Strategic Research Program in Epidemiology at Karolinska Institutet.

Reference

Anckarsater, H., Lundstrom, S., Kollberg, L., Kerekes, N., Palm, C., Carlstrom, E., . . . Lichtenstein, P. (2011). The Child and Adolescent Twin Study in Sweden (CATSS). *Twin Res Hum Genet, 14*(6), 495-508.

Becerra, T. A., Wilhelm, M., Olsen, J., Cockburn, M., & Ritz, B. (2013). Ambient air pollution and autism in Los Angeles county, California. *Environ Health Perspect, 121*(3), 380-386. doi: 10.1289/ehp.1205827

Bellander, T., Berglind, N., Gustavsson, P., Jonson, T., Nyberg, F., Pershagen, G., & Jarup, L. (2001). Using geographic information systems to assess individual historical exposure to air pollution from traffic and house heating in Stockholm. *Environ Health Perspect, 109*(6), 633-639.

Bhasin, T. K., & Schendel, D. (2007). Sociodemographic risk factors for autism in a US metropolitan area. *J Autism Dev Disord, 37*(4), 667-677. doi: 10.1007/s10803-006-0194-y

Block, M. L., & Calderon-Garciduenas, L. (2009). Air pollution: mechanisms of neuroinflammation and CNS disease. *Trends Neurosci, 32*(9), 506-516. doi: 10.1016/j.tins.2009.05.009

Burman, L., & Norman, M. (2013). The air quality in Stockholm: annual report 2012. Retrieved Feb 07, 2014, from http://www.slb.nu/slb/rapporter/pdf8/slb2013_005.pdf

Calderon-Garciduenas, L., Engle, R., Mora-Tiscareno, A., Styner, M., Gomez-Garza, G., Zhu, H., . . . D'Angiulli, A. (2011). Exposure to severe urban air pollution influences cognitive outcomes, brain volume and systemic inflammation in clinically healthy children. *Brain Cogn, 77*(3), 345-355. doi: 10.1016/j.bandc.2011.09.006

Calderon-Garciduenas, L., Solt, A. C., Henriquez-Roldan, C., Torres-Jardon, R., Nuse, B., Herritt, L., . . . Reed, W. (2008). Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid beta-42 and alpha-synuclein in children and young adults. *Toxicol Pathol, 36*(2), 289-310. doi: 10.1177/0192623307313011

Carlin, J. B., Gurrin, L. C., Sterne, J. A., Morley, R., & Dwyer, T. (2005). Regression models for twin studies: a critical review. *Int J Epidemiol, 34*(5), 1089-1099. doi: 10.1093/ije/dyi153

Dix-Cooper, L., Eskenazi, B., Romero, C., Balmes, J., & Smith, K. R. (2012). Neurodevelopmental performance among school age children in rural Guatemala is associated with prenatal and postnatal exposure to carbon monoxide, a marker for exposure to woodsmoke. *Neurotoxicology, 33*(2), 246-254. doi: 10.1016/j.neuro.2011.09.004

Flouri, E., Mavroveli, S., & Tzavidis, N. (2012). Cognitive ability, neighborhood deprivation, and young children's emotional and behavioral problems. *Soc Psychiatry Psychiatr Epidemiol, 47*(6), 985-992. doi: 10.1007/s00127-011-0406-4

Froehlich, T. E., Lanphear, B. P., Epstein, J. N., Barbaresi, W. J., Katusic, S. K., & Kahn, R. S. (2007). Prevalence, recognition, and treatment of attention-deficit/hyperactivity disorder in a national sample of US children. *Arch Pediatr Adolesc Med, 161*(9), 857-864. doi: 10.1001/archpedi.161.9.857

Gidhagen, L., Omstedt, G., Pershagen, G., Willers, S., & Bellander, T. (2013). High-resolution modeling of residential outdoor particulate levels in Sweden. *J Expo Sci Environ Epidemiol, 23*(3), 306-314. doi: 10.1038/jes.2012.122

Gillberg, C., Steffenburg, S., Borjesson, B., & Andersson, L. (1987). Infantile autism in children of immigrant parents. A population-based study from Goteborg, Sweden. *Br J Psychiatry, 150*, 856-858.

Greenland, S., & Brumback, B. (2002). An overview of relations among causal modelling methods. *Int J Epidemiol, 31*(5), 1030-1037.

Gruzieva, O., Bellander, T., Eneroth, K., Kull, I., Melen, E., Nordling, E., . . . Pershagen, G. (2012). Traffic-related air pollution and development of allergic sensitization in children during the first 8 years of life. *J Allergy Clin Immunol, 129*(1), 240-246. doi: 10.1016/j.jaci.2011.11.001

Guxens, M., Aguilera, I., Ballester, F., Estarlich, M., Fernandez-Somoano, A., Lertxundi, A., . . . Project, Inma. (2012). Prenatal exposure to residential air pollution and infant mental development: modulation by antioxidants and detoxification factors. *Environ Health Perspect, 120*(1), 144-149. doi: 10.1289/ehp.1103469

Hagberg, H., & Mallard, C. (2005). Effect of inflammation on central nervous system development and vulnerability. *Curr Opin Neurol, 18*(2), 117-123.

Hansson, S. L., Svanstrom Rojvall, A., Rastam, M., Gillberg, C., Gillberg, C., & Anckarsater, H. (2005). Psychiatric telephone interview with parents for screening of childhood autism - tics, attention-deficit hyperactivity disorder and other comorbidities (A-TAC): preliminary reliability and validity. *Br J Psychiatry, 187*, 262-267. doi: 10.1192/bjp.187.3.262

Jarbrink, K., Fombonne, E., & Knapp, M. (2003). Measuring the parental, service and cost impacts of children with autistic spectrum disorder: a pilot study. *J Autism Dev Disord, 33*(4), 395-402.

Jung, C. R., Lin, Y. T., & Hwang, B. F. (2013). Air pollution and newly diagnostic autism spectrum disorders: a population-based cohort study in taiwan. *PLoS One, 8*(9), e75510. doi: 10.1371/journal.pone.0075510

Kabir, Z., Connolly, G. N., & Alpert, H. R. (2011). Secondhand smoke exposure and neurobehavioral disorders among children in the United States. *Pediatrics, 128*(2), 263-270. doi: 10.1542/peds.2011-0023

Kogan, M. D., Strickland, B. B., Blumberg, S. J., Singh, G. K., Perrin, J. M., & van Dyck, P. C. (2008). A national profile of the health care experiences and family impact of autism spectrum disorder among children in the United States, 2005-2006. *Pediatrics, 122*(6), e1149-1158. doi: 10.1542/peds.2008-1057

Laaksonen, M., Rahkonen, O., Karvonen, S., & Lahelma, E. (2005). Socioeconomic status and smoking: analysing inequalities with multiple indicators. *Eur J Public Health, 15*(3), 262-269. doi: 10.1093/eurpub/cki115

Larson, T., Anckarsater, H., Gillberg, C., Stahlberg, O., Carlstrom, E., Kadesjo, B., . . . Gillberg, C. (2010). The autism--tics, AD/HD and other comorbidities inventory (A-TAC): further validation of a telephone interview for epidemiological research. *BMC Psychiatry, 10*, 1. doi: 10.1186/1471-244x-10-1

Magnusson, C., Rai, D., Goodman, A., Lundberg, M., Idring, S., Svensson, A., . . . Dalman, C. (2012). Migration and autism spectrum disorder: population-based study. *Br J Psychiatry, 201*, 109-115. doi: 10.1192/bjp.bp.111.095125

Martin, N., Scourfield, J., & McGuffin, P. (2002). Observer effects and heritability of childhood attention-deficit hyperactivity disorder symptoms. *Br J Psychiatry, 180*, 260-265.

Mills, N. L., Donaldson, K., Hadoke, P. W., Boon, N. A., MacNee, W., Cassee, F. R., . . . Newby, D. E. (2009). Adverse cardiovascular effects of air pollution. *Nat Clin Pract Cardiovasc Med, 6*(1), 36-44. doi: 10.1038/ncpcardio1399

Morales, E., Julvez, J., Torrent, M., de Cid, R., Guxens, M., Bustamante, M., . . . Sunyer, J. (2009). Association of early-life exposure to household gas appliances and indoor nitrogen dioxide with cognition and attention behavior in preschoolers. *Am J Epidemiol, 169*(11), 1327-1336. doi: 10.1093/aje/kwp067

Newton, C. R. (2012). Neurodevelopmental disorders in low- and middle-income countries. *Dev Med Child Neurol, 54*(12), 1072. doi: 10.1111/j.1469-8749.2012.04384.x

Nordling, E., Berglind, N., Melen, E., Emenius, G., Hallberg, J., Nyberg, F., . . . Bellander, T. (2008). Traffic-related air pollution and childhood respiratory symptoms, function and allergies. *Epidemiology, 19*(3), 401-408. doi: 10.1097/EDE.0b013e31816a1ce3

Panasevich, S., Leander, K., Rosenlund, M., Ljungman, P., Bellander, T., de Faire, U., . . . Nyberg, F. (2009). Associations of long- and short-term air pollution exposure with markers of inflammation and coagulation in a population sample. *Occup Environ Med, 66*(11), 747-753. doi: 10.1136/oem.2008.043471

Parr, J. R., Le Couteur, A., Baird, G., Rutter, M., Pickles, A., Fombonne, E., . . . International Molecular Genetic Study of Autism Consortium, Members. (2011). Early developmental regression in

autism spectrum disorder: evidence from an international multiplex sample. *J Autism Dev Disord, 41*(3), 332-340. doi: 10.1007/s10803-010-1055-2

Post codes and SAMS atlas. (2013). Retrieved October 08, 2013, from http://www.scb.se/Pages/Standard____333368.aspx

Ragland, D. R. (1992). Dichotomizing continuous outcome variables: dependence of the magnitude of association and statistical power on the cutpoint. *Epidemiology, 3*(5), 434-440.

Sandin, S., Lichtenstein, P., Kuja-Halkola, R., Larsson, H., Hultman, C. M., & Reichenberg, A. (2014). The familial risk of autism. *JAMA, 311*(17), 1770-1777. doi: 10.1001/jama.2014.4144

Sariaslan, A., Langstrom, N., D'Onofrio, B., Hallqvist, J., Franck, J., & Lichtenstein, P. (2013). The impact of neighbourhood deprivation on adolescent violent criminality and substance misuse: A longitudinal, quasi-experimental study of the total Swedish population. *Int J Epidemiol, 42*(4), 1057-1066. doi: 10.1093/ije/dyt066

Siddique, S., Banerjee, M., Ray, M. R., & Lahiri, T. (2011). Attention-deficit hyperactivity disorder in children chronically exposed to high level of vehicular pollution. *Eur J Pediatr, 170*(7), 923-929. doi: 10.1007/s00431-010-1379-0

The Swedish Medical Birth Register: a summary of content and quality. (2003). Retrieved Jan 27, 2014, from http://www.sos.se/fulltext/112/2003-112-3/2003-112-3.pdf

Van Leeuwen, W., Nilsson, S., & Merlo, J. (2012). Mother's country of birth and prescription of psychotropic medication in Swedish adolescents: a life course approach. *BMJ Open, 2*(5). doi: 10.1136/bmjopen-2012-001260

Windham, G. C., Zhang, L., Gunier, R., Croen, L. A., & Grether, J. K. (2006). Autism spectrum disorders in relation to distribution of hazardous air pollutants in the san francisco bay area. *Environ Health Perspect, 114*(9), 1438-1444.

Volk, H. E., Hertz-Picciotto, I., Delwiche, L., Lurmann, F., & McConnell, R. (2011). Residential proximity to freeways and autism in the CHARGE study. *Environ Health Perspect, 119*(6), 873-877. doi: 10.1289/ehp.1002835

Volk, H. E., Lurmann, F., Penfold, B., Hertz-Picciotto, I., & McConnell, R. (2013). Traffic-related air pollution, particulate matter, and autism. *JAMA Psychiatry, 70*(1), 71-77. doi: 10.1001/jamapsychiatry.2013.266

Vrijheid, M., Martinez, D., Aguilera, I., Bustamante, M., Ballester, F., Estarlich, M., . . . Project, Inma. (2012). Indoor air pollution from gas cooking and infant neurodevelopment. *Epidemiology, 23*(1), 23-32. doi: 10.1097/EDE.0b013e31823a4023

Tables

Table 1. Child and family characteristics in 9- and 12-year-old twins born in Stockholm

	Total	Healthy	ASD[a]	p[c]	ADHD[a]	p[c]	Non-respondents
N, %	3,426	3,051 (89.1)	109 (3.2)		328 (9.6)		1,554

Missing in neurodevelopmental outcomes			18		22		-
Child age at interview for respondents/ till year 2011 for non-respondents (mean±SD)	10.3±1.5	10.3±1.5	10.6±1.6		10.3±1.5		14.7±2.5
Respondent							
Biological mother	2,960 (86.4)	2,639 (86.5)	91 (83.5)		281 (85.7)		-
Biological father	450 (13.1)	401 (13.1)	14 (12.8)	‡	43 (13.1)		-
Other	16 (0.5)	11 (0.4)	4 (3.7)		4 (1.2)		-
Gender							
Male	1,756 (51.3)	1,510 (49.5)	80 (73.4)	‡	216 (65.9)	‡	733 (47.2)
Female	1,670 (48.7)	1,541 (50.5)	29 (26.6)		112 (34.2)		704 (45.3)
Parity							
First	791 (23.1)	703 (23.0)	30 (27.5)		80 (24.4)		264 (17.0)
Second	1,436 (41.9)	1,290 (42.3)	40 (36.7)		126 (38.4)		570 (36.7)
Third	845 (24.7)	755 (24.8)	24 (22.0)		80 (24.4)		408 (26.3)
Fourth or later	354 (10.3)	303 (9.9)	15 (13.8)		42 (12.8)		195 (12.5)
Zygosity							
Monozygosity	1,380 (40.3)	1,236 (40.5)	44 (40.4)		129 (39.3)		-
Dizygosity	1,742 (50.8)	1,551 (50.8)	58 (53.2)		166 (50.6)		-
Missing	304 (8.9)	264 (8.7)	7 (6.4)		33 (10.1)		-
Low gestation age(<37 weeks)							
Yes	1,360 (39.7)	1,193 (39.1)	55 (50.5)	‡	145 (44.2)	†	641 (41.2)
No	2,046 (59.7)	1,844 (60.4)	51 (46.8)		177 (54.0)		783 (50.4)
Missing	20 (0.6)	14 (0.5)	3 (2.7)		6 (1.8)		130 (8.4)
Low birth weight (<2,500g)							
Yes	1,287 (37.6)	1,129 (37.0)	48 (44.0)		138 (42.1)		620 (39.9)
No	2,082 (60.8)	1,868 (61.2)	60 (55.1)		187 (57.0)		792 (51.0)
Missing	57 (1.7)	54 (1.8)	1 (0.9)		3 (0.9)		142 (9.1)
Maternal age (mean±SD)	31.6±4.6	31.6±4.6	31.1±5.2		31.1±4.9	†	30.4±5.1

<25yrs	234 (6.8)	197 (6.5)	7 (6.4)		34 (10.4)		184 (11.8)
≥25yrs and <30yrs	838 (24.5)	737 (24.2)	39 (35.8)		89 (27.1)		418 (26.9)
≥30yrs and <35yrs	1,392 (40.6)	1,266 (41.5)	36 (33.0)	‡	110 (33.5)	†	521 (33.5)
≥35yrs	962 (28.1)	851 (27.9)	27 (24.8)		95 (29.0)		314 (20.2)
Maternal smoking during pregnancy							
No	2,591 (75.6)	2,334 (76.5)	77 (70.6)		220 (67.1)		1,041 (67.0)
Yes, 1-9 cigarettes/day	256 (7.5)	212 (7.0)	12 (11.0)		41 (12.5)		116 (7.5)
Yes, ≥10 cigarettes/day	164 (4.8)	132 (4.3)	8 (7.3)		29 (8.8)	‡	77 (5.0)
Missing	415 (12.1)	373 (12.2)	12 (11.0)		38 (11.6)		320 (20.6)
Maternal marital status at birth year							
Married or cohabiting	3,140 (91.6)	2,805 (91.9)	92 (84.4)		297 (90.6)		1,258 (81.0)
Single	270 (7.9)	231 (7.6)	17 (15.6)	†	30 (9.2)	†	165 (10.6)
Missing	16 (0.5)	15 (0.5)	0		1 (0.3)		131 (8.4)
Maternal marital status during child's 9th year of life							
Married or cohabiting	2,700 (78.8)	2,431 (79.7)	78 (71.6)		238 (72.6)		957 (61.6)
Single	604 (17.6)	510 (16.7)	26 (23.9)		79 (24.1)	†	350 (22.5)
Missing	122 (3.6)	110 (3.6)	5 (4.6)		11 (3.3)		247 (15.9)
Parental ethnicity							
Either one parent from Scandinavian countries	3,168 (92.5)	2,823 (92.5)	103 (94.5)		309 (94.2)		-
Both parents from other countries	258 (7.5)	228 (7.5)	6 (5.5)		19 (5.8)		-
Highest education by either parent (pregnancy)							
Low (≤9yrs)	218 (6.4)	183 (6.0)	17 (15.6)		31 (9.5)		179 (11.5)
Middle (10-12yrs)	1,382 (40.3)	1,191 (39.0)	58 (53.2)		167 (50.9)		541 (34.8)
High(>12yrs)	1,695 (49.5)	1,566 (51.3)	28 (25.7)	‡	115 (35.1)	‡	543 (34.9)
Missing	131 (3.8)	111 (3.6)	6 (5.5)		15 (4.6)		291 (18.7)

Highest education by either parent (1st year of life)						
Low (≤9yrs)	136 (4.0)	114 (3.7)	9 (8.3)		20 (6.1)	145 (9.3)
Middle (10-12yrs)	1,284 (37.5)	1,092 (35.8)	60 (55.1)	‡	170 (51.8)	‡ 545 (35.1)
High(>12yrs)	1,891 (55.2)	1,744 (57.2)	36 (33.0)		127 (38.7)	593 (38.2)
Missing	115 (3.4)	101 (3.3)	4 (3.7)		11 (3.4)	271 (17.4)
Highest education by either parent (9th year of life)						
Low (≤9yrs)	136 (4.0)	113 (3.7)	9 (8.3)		21 (6.4)	160 (10.1)
Middle (10-12yrs)	1,210 (35.3)	1,026 (33.6)	57 (52.3)	‡	161 (49.1)	‡ 565 (37.9)
High(>12yrs)	2,043 (59.6)	1,880 (61.6)	41 (37.6)		143 (43.6)	598 (41.2)
Missing	37 (1.1)	32 (1.1)	2 (1.8)		3 (0.9)	231 (14.9)
NPI at birth (mean±SD)	-0.1±1.0	-0.1±1.0	0.1±1.2		0.0±1.1	† 0.3 ±1.4
NPI during 9th year of life (mean±SD)	-0.3±0.9	-0.3±0.9	-0.2±1.1		-0.2±0.8	† 0.1 ±1.2
Individualized income during mother's pregnancy (mean±SD,1000 SEK)	105.0±110.8	106.8±116.3	86.7±35.9		89.8±44.3	† 89.2±63.6
Individualized income during child's 9th year of life (mean±SD,1000 SEK)	162.0±228.9	164.5±240.6	134.5±62.6		141.1±88.5	149.6±197.8
Comorbidity[b]						
Yes	120 (3.5)	59 (1.9)	44 (40.4)		48 (14.6)	75 (4.8)
No	3,306 (96.5)	2,992 (98.1)	65 (59.6)	‡	280 (85.4)	‡ 1,479 (95.2)

Definition of abbreviations: ASD=Autism Spectrum Disorders, ADHD= Attention Deficit/Hyperactivity Disorders, NPI=Neighborhood Deprivation Index, SD=Standard Deviation, SEK=Swedish kronor.

[a] Cut-off values of disorders from extended diagnostic criteria: ASD=4.5 and ADHD =6.0

[b] Comorbidity included co-occurrence with severe chromosome abnormalities, malformations of brain, epilepsy, cerebral palsy and other neurological disorders. Detailed information on diagnosis codes was listed in Table S1 in supplemental materials.

c The p-values were presented comparing ASD/ADHD individuals to ones with neither ASD nor ADHD. † indicates $p<0.05$ and ‡ indicates $p<0.001$.